

## Behavioral and Physiological Consequences of Sleep Restriction

Siobhan Banks, Ph.D. and David F. Dinges, Ph.D.

*Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA*

Adequate sleep is essential for general healthy functioning. This paper reviews recent research on the effects of chronic sleep restriction on neurobehavioral and physiological functioning and discusses implications for health and lifestyle. Restricting sleep below an individual's optimal time in bed (TIB) can cause a range of neurobehavioral deficits, including lapses of attention, slowed working memory, reduced cognitive throughput, depressed mood, and perseveration of thought. Neurobehavioral deficits accumulate across days of partial sleep loss to levels equivalent to those found after 1 to 3 nights of total sleep loss. Recent experiments reveal that following days of chronic restriction of sleep duration below 7 hours per night, significant daytime cognitive dysfunction accumulates to levels comparable to that found after severe acute total

sleep deprivation. Additionally, individual variability in neurobehavioral responses to sleep restriction appears to be stable, suggesting a trait-like (possibly genetic) differential vulnerability or compensatory changes in the neurobiological systems involved in cognition. A causal role for reduced sleep duration in adverse health outcomes remains unclear, but laboratory studies of healthy adults subjected to sleep restriction have found adverse effects on endocrine functions, metabolic and inflammatory responses, suggesting that sleep restriction produces physiological consequences that may be unhealthy.

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There is ample scientific evidence to support the conclusion that sleep is an essential physiological need state that must be satisfied to ensure survival.<sup>1-3</sup> Experimental work on sleep restriction has now begun to focus on the basic question of how much sleep people need each day to be healthy and safe. Chronic sleep restriction is frequently experienced due to medical conditions, sleep disorders, work demands, social and domestic responsibilities, and life style. This paper reviews recent research on the effects of chronic sleep restriction on neurobehavioral and physiological functioning relative to implications for health and safety.

### SLEEP DURATION

#### Population-Based Estimates of Sleep Duration

Habitual sleep duration among adults shows considerable variation within and between individuals.<sup>4</sup> The largest available database to date on self-reported sleep duration involved 1.116 mil-

lion Americans (age  $\geq 30$  years; mean = 57 years for women and 58 years for men)<sup>5</sup> who were queried about their sleep duration in 1982 as part of an American Cancer Society study. Sleep duration was distributed approximately normally, with 52.4% of subjects reporting  $< 7.5$  hours of sleep per night. In this sample, 19.7% of subjects reported sleeping  $< 6.5$  hours, and 4.0% reported sleeping  $< 5.5$  hours per night. At the other end of the spectrum, 9.2% of probands slept  $\geq 8.5$  hours, and 3.3% reported sleeping  $\geq 9.5$  hours per night. There were only very small differences in sleep duration between men and women in this study. It is not known to what extent these self-reported sleep durations accurately reflected physiologic sleep obtained, but this uncertainty plagues all epidemiological and survey studies of sleep duration. Since the data were acquired more than 24 years ago,<sup>5</sup> it is uncertain whether these sleep duration estimates can be interpreted as being consistent with more recent population trends of declining sleep duration.

A 2005 Gallup poll in the USA found that among 1,500 adults (age  $\geq 18$  years; mean = 49 years) the average self-reported sleep duration was 6.8 h on weekdays and 7.4 h on weekends.<sup>6</sup> However, there was considerable variation in reported sleep duration—16% of those interviewed reported sleeping  $< 6$  h per day on weekdays, while 10% did so on weekends.<sup>6</sup> The proportion of U.S. adults reporting that they slept  $\geq 8$  h on weekdays decreased by 9% from a 1998 poll to a 2005 poll, while those reporting  $< 6$  h of sleep on weekdays increased by 4% over the same time period.<sup>6</sup> Table 1 displays the results, which suggest that sleep duration as reported by American adults decreased over the past 8 years. There is considerable debate as to whether or not sleep duration has been decreasing among adults, and, if so, whether this is resulting in higher rates of chronic sleep restriction or sleep debt.<sup>7,8</sup>

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Address correspondence to: Siobhan Banks, Division of Sleep and Chronobiology, Unit for Experimental Psychiatry, Department of Psychiatry, University of Pennsylvania School of Medicine, 1013 Blockley Hall, 423 Guardian Drive, Philadelphia, PA, USA 19104-6021; Tel: (215) 898-9665; Fax: (215) 573-6410; E-mail: sbanks@mail.med.upenn.edu

**Table 1**—Percentage of Participants that Reported Sleep Times in 4 Categories on Weekdays and Weekends from the 1998 and 2005 National Sleep Foundation Gallop Polls.

Hours of sleep	1998		2005		diff.	
	weeknight	weeknight	weekend	weekend		
≥ 8	35	26	-9	53	49	-4
7-7.9	28	31	+3	23	24	+1
6-6.9	23	24	+1	14	15	+1
< 6	12	16	+4	8	10	+2

Data collected from N = 1506 participants (mean age 40.9 yr; 51% female) randomly selected based on U.S. Census household data (e.g., household has individuals over 18 yr).<sup>6</sup> Telephone interviews were conducted between September and November 2004. Values in the table are expressed as percentages. Over the years, respondents who reported sleeping  $\geq 7$  h on weeknights decreased from 63% in 1998 to 57% in 2005. Additionally, the percentage of people who reported sleeping  $> 7$  h on weekend nights has dropped from 76% in 1998 to 73% in 2005. Overall, there appears to be an increase in the percentage of people sleeping  $< 6$  h/night and a decrease in those sleeping  $> 7$  h/night both during the week and on weekends.

## NEUROBEHAVIORAL CONSEQUENCES OF SLEEP RESTRICTION

Unlike total sleep deprivation, which has been extensively investigated experimentally, the effects of partial sleep deprivation have received less scientific attention, even though sleep restriction is more prevalent as a result of medical conditions and sleep disorders, as well as lifestyle (e.g., shiftwork, jet lag, prolonged work hours).

Partial sleep deprivation can occur in 3 ways. The first involves preventing sleep from being physiologically consolidated and is referred to as sleep fragmentation, which can occur in certain sleep disorders (e.g., untreated obstructive sleep apnea). During sleep fragmentation, the normal progression and sequencing of sleep stages is typically disrupted to varying degrees, resulting in less time in consolidated physiological sleep, relative to time in bed. The second type of partial sleep deprivation involves loss of specific physiological sleep stages, and is, therefore, referred to as selective sleep stage deprivation. This is presumed to be less common than the other types, but prevalence estimates do not exist for any type of sleep restriction. Selective sleep stage deprivation can occur if sleep fragmentation is isolated to a specific sleep stage (e.g., when apneic episodes disrupt primarily one stage of sleep such as REM sleep, or when medications suppress a specific sleep stage). The third type of partial sleep deprivation is sleep restriction, which is also referred to as sleep debt,<sup>9</sup> which is characterized by reduced sleep duration. Sleep restriction is the focus of this review because it is common, it relates to the fundamental question of how much sleep people need, and there is considerable experimental evidence of its neurobehavioral and physiological effects. Of particular interest are the questions of what changes when sleep is steadily reduced from 8 hours' to 4 hours' duration each day (i.e., the range many people experience sleep restriction), and whether there are cumulative dose response effects of this reduction on sleep physiology and waking functions.

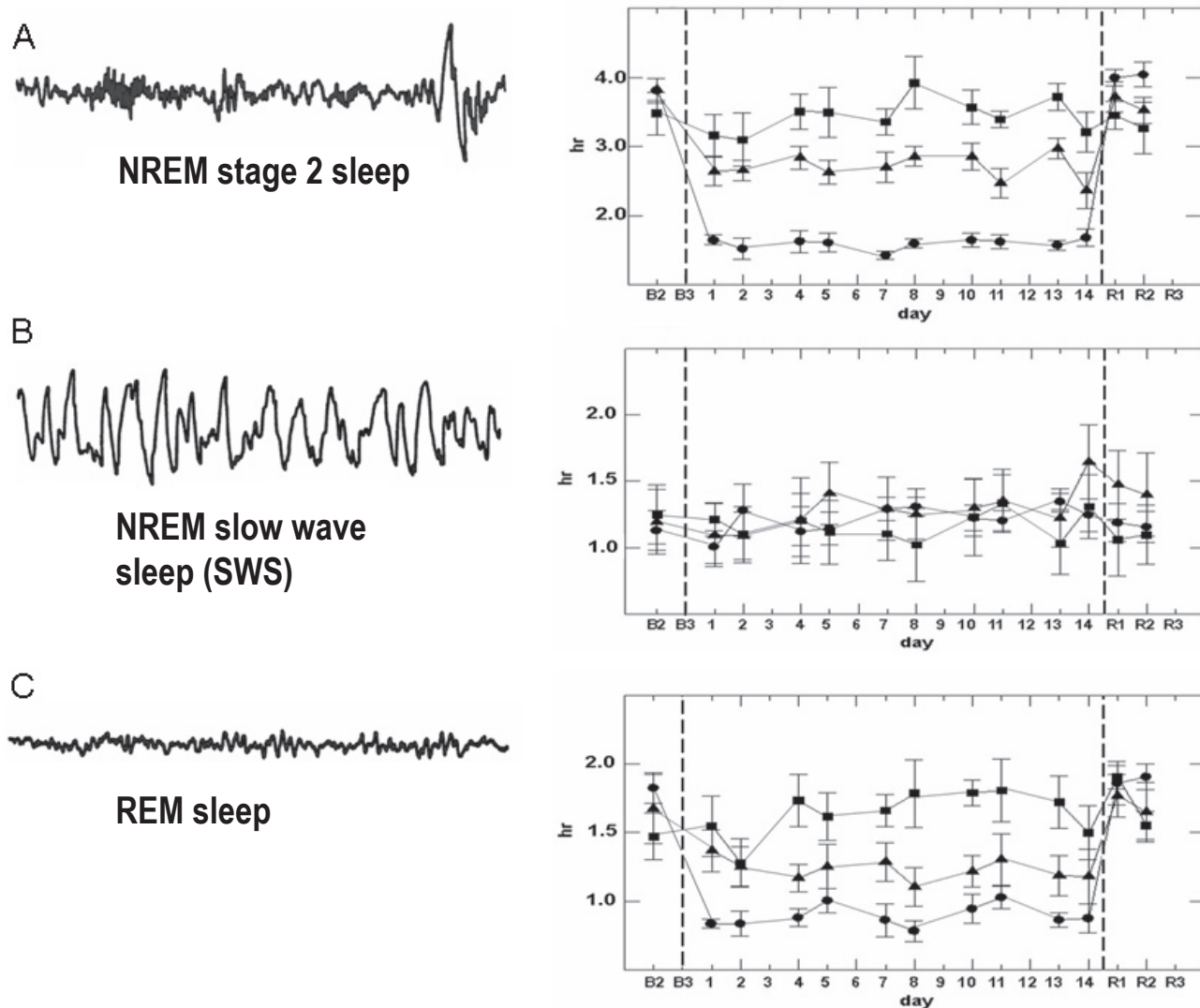
### Changes in Sleep Architecture During Sleep Restriction

Sleep restriction alters sleep architecture, but it does not affect all sleep stages equally. Depending on the timing and duration of

sleep, and the number of days it is reduced, some aspects of sleep are conserved, occur sooner, or intensify, while other aspects of sleep time are diminished. For example, healthy adults fell asleep more quickly and had decreased time in NREM stage 2 sleep and REM sleep when restricted to 4 h of nocturnal sleep for multiple nights, but they had no decrease in NREM slow wave sleep (SWS) relative to a typical 8-h nocturnal sleep period<sup>10-13</sup> (see Figure 1). While visually scored NREM SWS was conserved, slow wave sleep activity (SWA) derived from power spectral analysis of delta wave activity (0.5-4.0 Hz) in the EEG during NREM stages 2, 3, and 4 sleep showed some dynamic increases as restriction of sleep to 4 h continued for more than a day.<sup>11,12</sup> The conservation of SWS and intensification of SWA during sleep restricted to 4 h/night in healthy adults, has suggested the hypothesis that NREM EEG slow waves are essential and perhaps protected aspects of the physiological recovery afforded by sleep to waking brain functions. It remains to be determined whether the lack of SWS and SWA response to sustained (chronic) restriction of sleep to 4 h a night, relative to steady increases in physiological and neurobehavioral measures of sleepiness,<sup>12</sup> can account for the latter deficits. Neither SWS nor NREM SWA show the magnitude of increases following chronic sleep restriction observed following total sleep deprivation.<sup>12</sup> Consequently, while SWS and NREM SWA may be largely conserved in chronic sleep restriction to 4-7 hours per night, they do not appear to either reflect the severity of daytime cognitive deficits or prevent these deficits, raising serious doubts about SWS and NREM SWA as the only aspects of sleep critical to waking functions.

### Experimental Control of Wakefulness in Sleep Restriction Experiments

Experimental protocols that restrict healthy adult sleep duration across consecutive days provide the most appropriate paradigms for addressing the question of whether waking neurobehavioral deficits accumulate, and, if so, the rate of accumulation as the reduced sleep duration is maintained for multiple days. However, the cost and logistical complexities of maintaining tight experimental control over the sleep and waking activities of a large number of subjects, 24-hours a day for 1-3 weeks have resulted in only a few experiments on chronic sleep restriction being done in a scientifically sound manner. Most early experimental reports (before 1965) on the waking neurobehavioral effects of prolonged sleep restriction to durations people commonly experience (i.e., 4-6 h sleep per day) bordered on the anecdotal and lacked adequate sample sizes and control groups.<sup>9</sup> Subsequent experimental reports (1970-1995) on the cognitive and subjective effects of sleep restricted to 4-6 hours a night often failed to ensure that subjects maintained the assigned sleep-wake schedules; used infrequent, confounded and/or insensitive measures of sleep and waking; lacked sophisticated time series analyses; and generally drew conclusions not substantiated by the quantitative results (for reviews, see <sup>9,14,15</sup>). These methodological inadequacies and small sample sizes resulted in conflict as to whether or not sleep restriction resulted in cumulative waking cognitive and subjective changes, which prompted 3 widely repeated conclusions: (1) that reducing nightly sleep duration to between 4 and 6 h had little adverse effects on daily functions<sup>16-19</sup>; (2) that only a "core sleep" duration of 4-6 h was physiologically essential, and any additional sleep beyond that core duration was optional sleep



**Figure 1**—The effects of sleep restriction on NREM stage 2 sleep in Panel A; on NREM slow wave sleep (SWS) in Panel B; and on REM sleep in Panel C. Data are adapted from Van Dongen et al.<sup>12</sup> Following 8 hours of time in bed on baseline nights (B1, B2, B3), sleep was restricted for 14 consecutive nights to either 4 hours of time in bed (●, n = 13 healthy adults), 6 hours of time in bed (▲, n = 13), or 8 hours of time in bed (■, n = 9). Restriction was implemented by delaying bed time and holding sleep offset time constant (07:30). Sleep restriction nights were followed by 3 nights of 10 hours of time in bed for recovery sleep (R1, R2, R3). Sleep stages were scored polysomnographically for 2 out of every 3 nights during the experiment. Panel A: During the 14 nights of restriction to 4 h of time in bed, NREM stage 2 sleep was decreased an average of more than 2 h per night relative to the 8-h control condition ( $p < 0.001$ ). Stage 2 sleep was decreased approximately 1 h per night in the 6-h condition relative to the control condition ( $p < 0.001$ ). Panel B: In contrast to NREM stage 2 sleep, NREM slow wave sleep (SWS) showed no significant reduction in either the 4-h or 6-h sleep restriction conditions relative to the 8-h control condition. Panel C: Relative to the 8-h control condition, REM sleep was reduced by approximately 47 minutes a night during the 14 nights of restriction to 4 h time in bed ( $p < 0.01$ ), and by 24 minutes a night during the 14 nights of restriction to 6 h time in bed ( $p < 0.05$ ).

that reflected residual capacity<sup>9,20</sup>; and (3) that an individual could adapt to a reduced amount of sleep with few neurobehavioral consequences.<sup>20</sup> These conclusions were subsequently shown to be incorrect, as tightly controlled experiments on chronic partial sleep restriction failed to support them.<sup>10,12,15</sup> The results of these more recent, scientifically controlled studies will be discussed in following sections.

### Physiological Sleep Propensity During Sleep Restriction

The tendency to fall asleep is among the most well validated measures of sleepiness. It is based on the assumption that sleepiness is a physiologic need state that leads to an increased tendency to fall asleep, and it is operationalized as the speed of falling

asleep in both sleep-conductive and nonconductive conditions.<sup>21</sup>

The effects of chronic sleep restriction on daytime physiological sleep propensity has been evaluated using the multiple sleep latency test (MSLT)<sup>22</sup> and the maintenance of wakefulness test (MWT).<sup>23</sup> During the MSLT, the subject is instructed to close the eyes and try to fall asleep, while lying supine for 20-min periods, two hours apart, four to five times throughout the day, while polysomnography (PSG) recordings are made (these include EEG, EOG, and EMG). The MWT uses a similar protocol to the MSLT, but subjects are seated upright and instructed to try to stay awake. The time taken to fall asleep on both tests is a measure of sleep propensity.

The MSLT has been shown to vary linearly following a single night of sleep restricted to between 1 and 5 h of time in bed.<sup>24</sup>

In addition, the MSLT showed progressive shortening (i.e., more sleep propensity) when healthy young adults were restricted to 5 h of sleep a night for 7 consecutive nights.<sup>24</sup> This seminal finding of sleep propensity increasing across days of sleep restriction was confirmed in a later study using the psychomotor vigilance task as a measure of daytime behavioral alertness.<sup>15</sup>

Dose-response effects of chronic sleep restriction on daytime sleep propensity have also recently been found in an experiment on the effects of reduced nocturnal sleep dosages on daytime sleep latencies of commercial truck drivers.<sup>10</sup> A significant increase in sleep propensity across 7 days of sleep restricted to either 3 or 5 h per night was observed, with no differences found when sleep was restricted to 7 or 9 h per night.<sup>10</sup> Sleep propensity, as measured by the MWT, has also been found to increase in experiments in which adults were restricted to 4 h for sleep for 7 nights<sup>13,25</sup> and for 5 nights.<sup>13,25</sup>

In an epidemiological study of predictors of objective sleep tendency in the general population,<sup>26</sup> a dose-response relationship was found between self-reported nighttime sleep duration and objective sleep tendency as measured by MSLT. Persons reporting >7.5 hours of sleep had significantly less probability of falling asleep on the MSLT than those reporting to between 6.75 to 7.5 h per night (27% risk of falling asleep) and than those reporting sleep durations less than 6.75 h per night (73% risk of falling asleep).<sup>26</sup> Consequently, to date, studies consistently suggest that chronic curtailment of nocturnal sleep increases daytime sleep propensity.

Sleep loss has also been found to affect oculomotor responses. Eyelid closure and slow rolling eye movements are part of the initial transition from wake to drowsiness and light sleep (i.e., stage 1 sleep). Eye movements and eye closures have been studied during sleep loss protocols, under the premise that increases in the number and duration of slow eye movements and slow eyelid closures are reflections of increased sleep tendency. It has been demonstrated experimentally that slow eyelid closures during performance demands reliably track lapses of attention on a vigilance task<sup>27,28</sup> and during simulated driving.<sup>29,30</sup> Chronic sleep restriction has been reported to lead to a decrease in saccadic velocity in subjects allowed only 3 h or 5 h of time in bed for sleep over 7 nights, and an increase in the latency to pupil constriction.<sup>10</sup> These changes in oculomotor activity were positively correlated with sleep latency, subjective sleepiness measures, and accidents on a simulated driving task.<sup>31</sup>

### Effects of Sleep Reduction on Behavioral Alertness and Cognitive Performance

Restricted sleep time affects many different aspects of waking cognitive performance, but especially behavioral alertness.<sup>32</sup> Performance on psychomotor vigilance tasks requiring vigilant attention is very sensitive to sleep loss in general and sleep restriction in particular.<sup>33,34</sup> Many experiments have demonstrated that sleep deprivation increases behavioral lapses during performance,<sup>33,34</sup> which are assumed to reflect microsleeps.<sup>35,36</sup> As sleep loss continues, lapses can range in duration from 0.5 seconds to well over 10 sec, and they can progress to full blown sleep attacks (i.e., lapses from which subjects will not spontaneously arise without additional stimulation).<sup>35,36</sup> It has been hypothesized<sup>37,38</sup> that the lapses produced by sleep loss may originate in sleep-initiating subcortical systems (e.g., hypothalamus, thalamus, and brainstem).<sup>39</sup> This

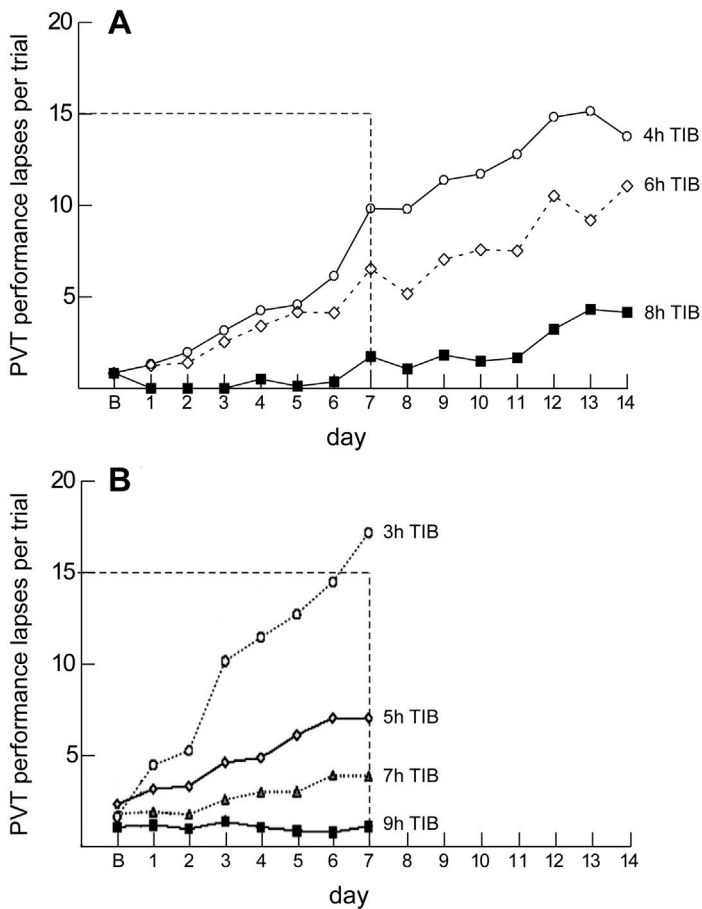
has been conceptualized as “wake state instability,”<sup>33,34,37</sup> which refers to moment-to-moment shifts in the relationship between neurobiological systems mediating wake maintenance and those mediating sleep initiation.<sup>39,40</sup> Behavioral alertness as measured by psychomotor vigilance tasks—or other sustained attention tasks—has proven to be very sensitive to sleep restriction.<sup>35,37,38</sup>

The 2 most extensively controlled experiments on chronic sleep restriction in healthy adults have found systematic evidence that behavioral alertness—as measured by psychomotor vigilance testing<sup>35,36</sup>—deteriorated steadily across days when nightly sleep duration was between 3 and 7 h,<sup>10</sup> with deterioration being more rapid as time allowed for sleep was reduced. In the experiment by Belenky and colleagues,<sup>10</sup> commercial truck drivers were kept in the laboratory for 14 d and randomized to seven nights of 3, 5, 7, or 9 h in bed for sleep per night. Those in the 3- and 5-h conditions had growing daytime deficits over the week in response to speed and number of lapses on the psychomotor vigilance task (PVT).<sup>10</sup> Subjects allowed 7 h/night had a significant decrease in PVT response speed. In contrast, performance in the group allowed 9 h time in bed was stable over the week. A similar experiment completed in our laboratory<sup>12</sup> kept healthy adults (mean age 28 y) in the laboratory for 20 days, randomizing them to either 4, 6, or 8 h time in bed per night for 14 consecutive nights. Psychomotor vigilance test performance and working memory performance were tested every 2 hours throughout each day. Cumulative daytime deficits in both PVT and cognitive throughput were observed for the 4- and 6-h sleep restriction conditions, but not the 8-h condition. In order to quantify the magnitude of cognitive deficits experienced during 14 days of restricted sleep, the effects of sleep restriction were compared to 1, 2, and 3 nights of total sleep deprivation.<sup>12</sup> This comparison revealed that both 4- and 6-h sleep periods resulted in the development of impairments of behavioral alertness that increased to levels found after 1, 2, and even 3 nights of total sleep deprivation.<sup>12</sup>

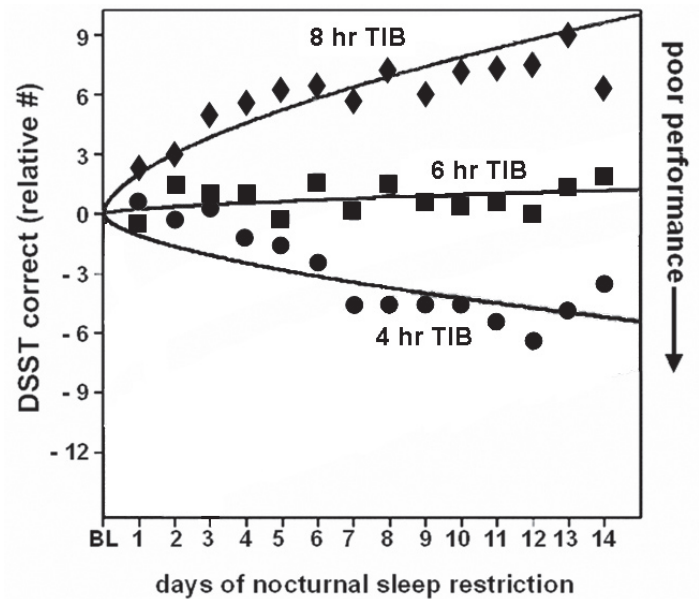
Figure 2 shows the number of PVT lapses per test bout each day from both of these controlled large-scale dose-response sleep-restriction experiments.<sup>10,12</sup> The remarkable similarity and internal consistency of the dependence of severity of PVT lapsing on the chronic sleep dose suggests that when the nightly sleep period is restricted to  $\leq 7$  h, healthy adults have increasing numbers of lapses of attention in proportion to the dose of sleep allowed (between subjects) and the number of days of sleep restriction (within subjects). A similar finding was observed for cognitive throughput performance on a working memory task,<sup>12</sup> which is shown in Figure 3.

The cognitive performance findings from these 2 major laboratory-based dose-response experiments on the effects of chronic sleep restriction in healthy adults are consistent with those on the effects of sleep restriction on physiological sleep propensity measures (MSLT, MWT) described above.<sup>10,13,24,25</sup> Collectively they suggest that there is a neurobiological integrator that either accumulates homeostatic sleep drive or the neurobiological consequences of excess wakefulness.<sup>10,12</sup> There has as yet been no definitive evidence of what is accumulating and destabilizing cognitive functions over time when sleep is regularly restricted to less than 7 hours per night, but one intriguing line of evidence suggests that it may involve extracellular adenosine in the basal forebrain.<sup>41-43</sup>

Although functional neuroimaging of cognitive changes produced by total sleep deprivation have been extensively studied,<sup>44,45</sup>



**Figure 2**—The effects of varying doses of nocturnal sleep time on lapses of attention from the psychomotor vigilance test (PVT). Panel A from Van Dongen et al.<sup>12</sup> involved experimental sleep restriction of  $n = 36$  healthy adults for 14 consecutive nights. In this experiment sleep was restricted for 14 consecutive nights. Subjects were randomized to 4 h time in bed ( $n = 13$ ), 6 h time in bed ( $n = 13$ ), or 8 h time in bed ( $n = 9$ ). PVT performance was assessed every 2 h (9 times each day) from 07:30 to 23:30. The graph shows systematic increases in lapses of sustained attention when sleep was restricted to either 4 h ( $p < 0.001$ ) or 6 h ( $p < 0.001$ ) per night, but not when sleep was restricted to 8 h per night ( $p = 0.29$ ). The increase in lapsing was worse in the 4-h sleep condition than in the 6-h sleep condition ( $p = 0.036$ ), further supporting a dose-response relationship within and between conditions. The horizontal dotted line shows the level of lapsing found in a separate experiment when subjects had been awake continuously for 64–88 h. For example, by day 7, subjects in the 6-h sleep restriction condition averaged 54 lapses (6 lapses  $\times$  9 test times) that day, while those in the 4-h sleep condition averaged 70 lapses that day. Panel B shows comparable sleep restriction data from Belenky et al.<sup>10</sup> In this study sleep was restricted for 7 consecutive nights in  $n = 66$  healthy adults. They were randomized to 3 h time in bed ( $n = 13$ ), 5 h time in bed ( $n = 13$ ), 7 h time in bed ( $n = 13$ ), or 9 h time in bed ( $n = 16$ ). Performance was assessed 4 times each day from 09:00 to 21:00. PVT lapses increases steadily across days in the 3-h ( $p = 0.001$ ) and 5-h ( $p = 0.001$ ) sleep restriction conditions (PVT response speed, but not lapses, was reduced in the 7-h condition, not shown). As in Panel A, the horizontal dotted line shows the level of lapsing found in a separate experiment when subjects had been awake continuously for 64–88 h.<sup>12</sup> Considering data in both Panels A and B, it is clear that restriction of nocturnal sleep time to  $< 7$  h per night in healthy adults results in systematic increases in lapses of waking attention that get progressively worse across days, in a dose-response manner.

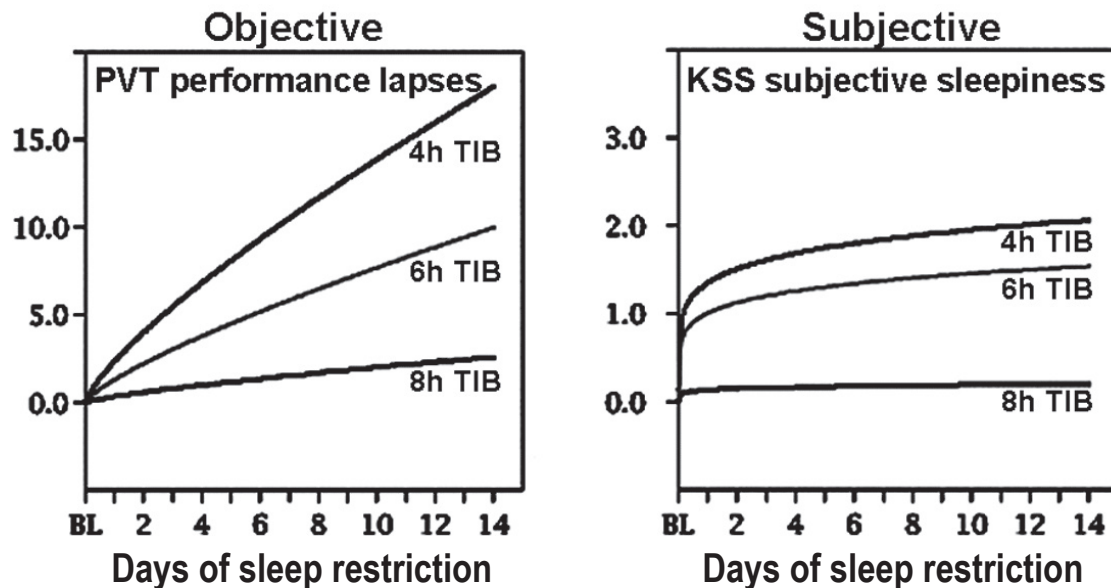


**Figure 3**—Digit symbol substitution task (DSST) performance responses to varying doses of daily sleep across 14 days. Data from  $n = 35$  subjects (8h condition  $n = 9$ , 6h condition  $n = 13$  and 4h condition  $n = 13$ ). Mean DSST per day (07:30–23:30), measured at 2-h intervals expressed relative to baseline (BL). The curves represent statistical nonlinear model-based best-fitting profiles of the DSST performance response to sleep loss. Adapted from Van Dongen et al.<sup>12</sup>

there are as yet no experimental reports on the effects of chronic sleep restriction on brain activation. While the neurobehavioral effects of chronic sleep restriction appear similar to those of total sleep deprivation,<sup>12</sup> the primary physiologic measure of homeostatic sleep—slow wave activity in the spectrally analyzed NREM EEG—shows a much more muted response to the former than to the latter, suggesting that there may be a different neurobiological mechanisms sub-serving the adverse effects of chronic sleep restriction.

### Sleep Restriction Effect on Subjective Reports of Sleepiness and Mood

Like NREM SWA, subjective sleepiness responses during chronic sleep restriction show a different dynamic profile than those found for total sleep deprivation. While the latter results in immediate increases in feelings of sleepiness, fatigue and cognitive confusion, with concomitant decreases in vigor and alertness<sup>21,35,36,38,46,47</sup> chronic sleep restriction yields much smaller changes in these psychometric ratings of internal state.<sup>10,12</sup> Thus, in contrast to the continuing accumulation of cognitive performance deficits associated with nightly restriction of sleep  $< 8$  h, ratings of sleepiness repeatedly made by subjects on standardized sleepiness scales did not parallel performance deficits.<sup>12</sup> As a consequence, after a week or two of sleep restriction, subjects were markedly impaired and less alert, but rated themselves subjectively as only moderately sleepy (see Figure 4). This suggests that people frequently underestimate the cognitive impact of sleep restriction and overestimate their performance readiness when sleep restricted. Other experiments using driving simulators have found comparable results.<sup>48</sup>



**Figure 4**—Data from  $n = 35$  subjects (8h condition  $n = 9$ , 6h condition  $n = 13$  and 4h condition  $n = 13$ ). Restriction of nocturnal sleep in healthy adults resulted in near-linear increases in Psychomotor Vigilance Test (PVT) lapses of attention across 14 days (coefficients of change near 1.0), but subjective ratings of sleepiness and fatigue (regardless of the psychometric scale used) showed a nonlinear coefficient below 0.5 for change over days. This meant that as objective performance continued to decline near-linearly, there were only minor further increases in the subjective ratings of sleepiness. By the end of the 14 days of sleep restriction, when performance was at its worst levels, subjects in the 4-h and 6-h sleep period conditions reported feeling only slightly sleepy. Therefore, unlike performance measures, sleepiness ratings appeared to show adaptation to chronic partial sleep deprivation. The lack of reports of intense feelings of sleepiness during chronic sleep restriction may explain why sleep restriction is widely practiced—people have the subjective impression they have adapted to it because they do not feel particularly sleepy. Adapted from Van Dongen et al.<sup>12</sup>

### Driving and Simulated Driving Following Sleep Reduction

One real-world risk associated with sleep restriction is decreased driving ability. Studies have primarily focused on the effects of short-term sleep restriction on driving ability and crash risk.<sup>49,50</sup> An epidemiological study found an increased incidence of sleep-related crashes in drivers reporting  $<7$  h of sleep per night on average.<sup>51</sup> Additional contributing factors to these crashes included poor sleep quality, dissatisfaction with sleep duration (i.e., undersleeping), daytime sleepiness, previously driving drowsy, amount of time driving and time of day (i.e., driving late at night). Studies have also examined the effects of sleep restriction on performance on various driving simulators. It has been found that driving performance decreased (e.g., more crashes) and subjectively reported sleepiness increased when sleep was restricted to between 4 and 6 h per night.<sup>31,48,52-57</sup>

### Individual Differences in Responses to Sleep Restriction

Interindividual variability in sleep and circadian parameters are substantial, and this is equally the case for neurobehavioral and physiological responses to sleep deprivation.<sup>4,21,31,35-38,46,47</sup> Sleep loss not only increases cognitive performance variability within subjects (intrasubject variability that is characterized as state instability),<sup>21,35,36,38,46,47</sup> but it also exposes marked neurobehavioral differences between subjects. That is, as sleep loss continues over time, intersubject differences in the degree of cognitive deficits also increase markedly.<sup>31,37</sup> This interindividual variability is also seen in responses to experimentally restricted sleep. For example, while sleep duration limited to less than 7 h per day resulted in cumulative cognitive performance deficits in a majority of healthy adults,<sup>10,12</sup> not everyone was affected to the same degree.<sup>10,12</sup> At

opposite ends of the spectrum are those who experience very severe impairments even with modest sleep restriction versus those who show few if any neurobehavioral deficits until sleep restriction is severe (in duration or chronicity). Moreover, there is some data to suggest that the nature of the cognitive impairments can be quite different among subjects for different cognitive tasks,<sup>9,58</sup> such that those with increasing problems performing working memory tasks may not have problems with psychomotor vigilance. Recently, and perhaps most importantly for future studies of the possible genetic contributors to differential vulnerability to sleep loss, is the finding that the neurobehavioral responses to sleep deprivation were stable and reliable within subjects,<sup>59</sup> suggesting they were trait-like.<sup>58,59</sup> The biological bases of differential responses to sleep loss are not known, although recent neuroimaging studies suggest that it may be possible to predict them before subjects are deprived of sleep.<sup>45,60,61</sup>

In summary, when sleep duration in healthy adults was experimentally reduced  $<7$  h per night, many waking neurobehavioral functions progressively deteriorated. A range of cognitive tasks (e.g., decision making) and normal daily behaviors (e.g., driving) were adversely affected by reduced sleep time.<sup>35,38,46,47,50</sup> These adverse neurobehavioral effects of sustained sleep restriction have the potential to lower productivity and increase the risks for errors and accidents.

### PHYSIOLOGICAL CONSEQUENCES OF SLEEP RESTRICTION

As noted above, recent epidemiological studies have found that both relatively long sleepers ( $\geq 8$  h sleep per day) and relatively short sleepers ( $<7$  h sleep per day) had increased risks of all-cause mortality.<sup>5,62,63</sup> There is also epidemiological evidence that reduced sleep duration is associated with larger body mass

index (BMI).<sup>64,65</sup> Laboratory studies of experimental restricted sleep in healthy adults suggest some mechanisms by which sleep duration may influence obesity, morbidity, and mortality.

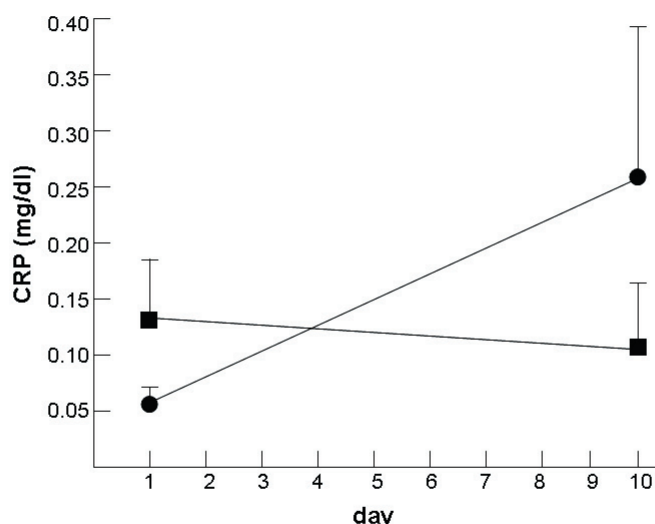
A range of physiological indices have been found to be altered by reduced sleep time. While the clinical significance of these findings in healthy adults is unknown, the indices affected have been related to health outcomes in patient populations. Several studies have reported an increased incidence and risk of medical disorders and health dysfunction related to shift work schedules, which have been attributed to both circadian disruption and sleep disturbance (for review, see <sup>66</sup>). Short-term sleep restriction results in a number of abnormal physiologic changes, including reduced glucose tolerance,<sup>67</sup> increased blood pressure,<sup>68</sup> activation of the sympathetic nervous system,<sup>69</sup> reduced leptin levels,<sup>70</sup> and increased inflammatory markers.<sup>71</sup> Although the magnitude of the physiologic changes found in these short-term studies was modest, the changes provide a potential mechanism whereby long-term sleep restriction may affect health.

### Endocrine Responses

A number of recent studies have focused on endocrine and metabolic consequences of chronic sleep restriction. Comparison of sleep restriction (4 h/night for 6 nights) to sleep extension (12 h/night for 6 nights) in healthy young adults revealed an elevation in evening cortisol, increased sympathetic activation, decreased thyrotropin activity, and decreased glucose tolerance in the restricted versus extended sleep condition.<sup>67</sup> Similarly, an elevation in evening cortisol levels, and advance in the timing of the morning peak in cortisol, so that the relationship between sleep termination and cortisol acrophase was maintained, was found following 10 nights of sleep restricted to 4.2 h time in bed for sleep each night compared to baseline measures and a control group allowed 8.2 h time in bed for sleep for 10 nights.<sup>72</sup> In the same protocol, a significant delay in melatonin onset<sup>73</sup> and in the timing of the peak in growth hormone, equivalent to the delay in sleep onset induced to achieve the restricted sleep period, were found, with no effect on growth hormone levels during the sleep period.<sup>74</sup>

Changes in the timing of the growth hormone secretory profile associated with sleep restriction to 4 h per night for 6 nights, with a bimodal secretory pattern have also been reported.<sup>75</sup> Decreased leptin levels (adipocyte-derived hormone that suppresses appetite) and increased ghrelin (predominantly a stomach-derived peptide that stimulates appetite) have been reported when sleep was restricted to 4 h a night relative to a 12-h control condition.<sup>70,76</sup> These effects are similar to what has been found for total sleep deprivation.<sup>77</sup> Thus, it is possible that sleep restriction produces alterations in the secretory profiles of appetite-regulating hormones, which in turn alter the signaling of hunger and appetite and promote increased weight gain and obesity.<sup>76</sup>

The possibility that sleep restriction may be associated causally with obesity by altered regulation of appetite-regulating hormones has also been suggested by findings of a study of 1,024 volunteers from the Wisconsin Sleep Cohort Study—a population-based longitudinal study of sleep disorders.<sup>64</sup> In this study, participants underwent nocturnal polysomnography and reported on their sleep habits through questionnaires and sleep diaries. Following polysomnography, morning fasted blood samples were evaluated for serum leptin, ghrelin, adiponectin, insulin, glucose, and lipid profile. Relationships among these



**Figure 5**—Mean (SEM) plasma high-sensitivity C-reactive protein (CRP) in  $n = 4$  subjects undergoing 10 consecutive nights of sleep restricted to 4.2 h time in bed, and in  $n = 5$  control subjects who had 10 consecutive nights of sleep restricted to 8.2 h time in bed (closed squares). Significance of difference in change from baseline to day 10 between groups ( $p = 0.08$  for interaction) by mixed-models analysis of variance on log-transformed data: the change from baseline to day 10 for the 4-h sleep restriction group was significant ( $p = 0.05$ ), whereas the change from baseline to day 10 in the 8-h control group was not ( $p = 0.72$ ). Figure adapted from Meier-Ewert et al.<sup>71</sup>

measures, BMI, and sleep duration revealed a curvilinear (U-shaped) association between sleep duration and BMI. In persons sleeping  $<8$  hours (74.4% of the sample), increased BMI was proportional to decreased sleep duration. Short sleep was associated with low leptin and high ghrelin independent of BMI. Since reduced leptin and elevated ghrelin are likely to increase appetite, this may explain the increased BMI observed with short sleep duration and how chronic sleep curtailment could contribute to obesity.<sup>13</sup>

### Immune Responses

The potential impact of chronic sleep restriction on immune responses has received little attention, although total sleep deprivation has been shown to activate non-specific host defense mechanisms and to elevate certain inflammatory cytokines (IL-6, TNF) in healthy young adults.<sup>78,79</sup> Although the effects of sleep restriction on cellular and humoral immune responses are largely unexplored, antibody production to vaccination has been reported to be decreased by sleep restriction. In one study it was reported that antibody titers were decreased by more than 50% 10 days post-vaccination for influenza.<sup>80</sup> Subjects had been vaccinated immediately following 6 nights of sleep restricted to 4 h per night compared to those who were vaccinated following habitual sleep duration. By 3-4 weeks post-vaccination, there was no difference in antibody levels between the 2 groups. In another study, attenuation of the febrile response to an endotoxin (*E. coli*) challenge in subjects undergoing chronic sleep restriction to 4 h/night for 10 nights (relative to subjects allowed 8 h for sleep) was observed.<sup>81</sup>

These two limited studies suggest that sleep restriction alters the acute immune response to vaccination, and decreases the febrile response to an endotoxin signal.

In a third experiment in which healthy young adults had their sleep restricted to 6 h per night, the 24-h secretory profile of IL-6 was increased in both sexes and TNF-alpha was increased in men.<sup>82</sup> Both IL-6 and TNF-alpha are markers of systemic inflammation that may lead to insulin resistance, cardiovascular disease and osteoporosis.<sup>83</sup>

### Cardiovascular Responses

An increase in cardiovascular events and cardiovascular morbidity associated with reduced sleep durations has been reported in a number of epidemiological studies<sup>5,62,84-87</sup> and in a case-control study examining insufficient sleep due to work demands.<sup>88</sup> In the Nurses' Health Study, there was evidence of increased risk of coronary events in female subjects obtaining  $\leq 7$  h sleep per night compared to those averaging 8 h per night.<sup>62</sup> In another epidemiological study, a 2-3-fold increase in risk of cardiovascular events was found for subjects with an average sleep duration of  $\leq 5$  h per night (or chronically having  $< 5$  h of sleep per night at least twice per week) was reported.<sup>88</sup> Similar findings have also been observed in studies examining cardiovascular health in shift workers, who typically experience chronic reductions in sleep duration, in addition to circadian disruption.<sup>89-92</sup>

The mechanisms underlying the link between chronic sleep restriction and increased cardiovascular risk are unknown; however, one potential mechanism may be by activation of inflammatory processes during sleep loss, as described above. C-reactive protein (CRP) is an inflammatory marker that is positive predictor of increased risk for cardiovascular disease.<sup>93</sup> We have found that high-sensitivity CRP was increased in healthy adults following both total sleep deprivation and chronic sleep restriction.<sup>71</sup> Figure 5 illustrates these findings. It remains to be determined how chronic sleep restriction activates mechanisms involved in cardiovascular morbidity and mortality, but elevated CRP may be a link.

### CONCLUSION

Restricted sleep time—particularly when chronic can cause significant and cumulative neurobehavioral deficits and physiological changes, some of which may account for the epidemiological findings that reduced sleep durations are associated with obesity, cardiovascular morbidity, traffic accidents and death. Recent careful controlled experiments in healthy adults reveal that as sleep was repeatedly restricted to less than 7 h per night, significant daytime cognitive dysfunction (i.e., state instability, reduced vigilant attention and working memory) accumulated as restriction continued to levels comparable to that found after severe acute total sleep deprivation. This strongly suggests the existence of a neurobiological integrator in the brain that instantiates either the need for sleep across days or the accumulation of excess wakefulness. These experiments also reveal that individuals differ markedly in their cognitive vulnerabilities to sleep restriction, which suggests a trait-like (possibly genetic) basis for the response. Research also demonstrates that experimentally induced chronic sleep restriction results in several adverse physiologic consequences, including reduced glucose tolerance,

increased blood pressure, and increased inflammatory markers in healthy adults. Consistent with these reports are epidemiologic studies that find self-reported short sleep duration is associated with obesity, heart disease, and mortality. Thus, current research findings on the effects of sleep restriction on neurobehavioral and physiological functioning suggest that adequate sleep duration (7-8 hours per night) is vital.

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